

DERIVATIVES OF PIPERAZINE III

BY

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REVIEW OF LITERATURE AND INTRODUCTION

Syntheses involving the amino groups of the piperazine molecule have been varied in nature. For the most part they have been confined to reactions involving the formation of monoacyl, monoary, diacyl and diaryl derivatives. An extensive review of such syntheses has been given by Adelson¹. Much work has likewise been done on derivatives of piperazine with various types of organic acids by Pollard and Adelson², Adelson¹ and Pollard, Adelson and Bain³. The latter authors⁴ have also investigated reactions of piperazine with unsaturated esters. No attempt will be made here to recapitulate the aforementioned investigations. For details of these projects the reader is referred to the appropriate references given above.

Van Dorp⁵ was unsuccessful in his attempts to prepare piperazino-1,4-bis (ethyl acetate) and piperazino-1,4-bis (methyl acetate). Franchimont and Kramer⁶ succeeded in preparing the sulfates of these esters by refluxing the mono-sulfate of piperazino-1,4-bis (acetic acid) and the appropriate alcohol for four hours. The desired esters were obtained from the sulfates by treatment with potassium carbonate in benzene solution and subsequent evaporation of the solvent. The yields reported were from fifty to sixty per cent of theoretical.

Van Dorp⁵ and subsequently Franchimont and Kramer⁶ prepared piperazino-1,4-bis (ethanenitrile) by the interaction of piperazine hexahydrate, methanal, potassium cyanide and acetic acid in aqueous solution. After twenty-four hours the formation of the desired product was com-

plete.

The same authors prepared piperazino-1,4-bis (ethanamide) from piperazino-1,4-bis (ethanenitrile) by the method of Münch.⁷ This consisted in dissolving the latter compound in an excess of concentrated sulfuric acid, allowing to stand for twenty-four hours, and subsequently removing the sulfuric acid by means of barium hydroxide. The yields were not reported.

Piperazino-1,4-bis (acetic acid) was obtained by Van Dorp⁵ by boiling piperazino-1,4-bis (ethanenitrile) with an excess of aqueous barium hydroxide until evolution of ammonia had ceased. This required several hours. The barium ion was removed as barium sulfate by treatment with sulfuric acid. Here again no yield was reported.

A preliminary report of the work of Franchimont and Kramer⁸ was published in 1909 soon after publication of the researches of Van Dorp⁵.

A search of the recorded literature has revealed no derivatives of N-phenyl-piperazine similar to those reported in this dissertation. Prelog and Blazek⁹ have prepared the mono- and di-hydrobromides of N-phenyl-piperazine-N'-ethyl acetate; they have not converted these to the free base.

A little over half of the experimental part of the present dissertation is concerned with reactions of the amino hydrogens of piperazine with the chlorine of various derivatives of monochloroacetic acid, e.g., the esters, the nitrile, the amide, the sodium salt and the corresponding alcohol. In all cases the compounds obtained are di-substituted piper-

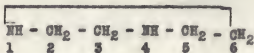
sine derivatives. Optimum conditions for syntheses have been investigated and the interconversion of one type of compound into another has been studied. In all cases where previously known compounds have been made, improved methods of synthesis involving shorter intervals of time and better yields have been used. A corresponding series of compounds of N-phenyl-piperazine²³ and derivatives of monochloroacetic acid has been made. None of the latter have previously been reported. A comparison of the piperazine and N-phenyl-piperazine compounds has likewise been made.

NOMENCLATURE

It is possible in organic chemistry to give several names to the same compound. This state of affairs has on the one hand the great advantage of permitting clear expression of thought and of rendering it easier to bring out analogies in structure wherever this is useful. On the other hand, however, the multiplicity of names for the same substance constitutes a serious obstacle both in the preparation of indexes and in the intelligent interpretation of the terminology of a particular phase of organic chemistry with which the reader is not overly familiar.

With the above in mind this dissertation has been written and the compounds described therein have been named in accordance with the "Definitive Report of the Commission on the Reform of Nomenclature of Organic Chemistry"²⁴. In like fashion nomenclature used in reference to compounds that are mentioned in the Review of Literature and Introduction and in the Preparation of Intermediates is not necessarily the same as it appears in the older original references cited in the Bibliography. Such compounds have likewise been named in keeping with the above mentioned report.²⁴

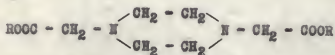
The official Chemical Abstracts Formula for piperazine is



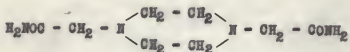
Derivatives in which the substituent groups are attached to the nitrogen atoms are termed either 1,4-derivatives of piperazine or N,N'-derivatives of piperazine. Both methods of nomenclature are used in this

dissertation. Univalent radicals derived from heterocyclic compounds by removal of hydrogen from the ring are usually named by changing their endings to yl. Inasmuch as this may cause some ambiguity as to whether or not the hydrogen has been removed from a carbon atom or a nitrogen atom, the name "piperasino" has been adopted in preference to "piperasiny" or "piperazy" for cases where hydrogen has been removed from the amino nitrogens of piperazine. Such choice is supported by the fact that the word "piperasino" has been accepted in such capacity in publications in the Journal of the American Chemical Society⁴ and has been used in Chemical Abstracts,²⁵ The prefix "bis" has been applied in keeping with the rules set forth by the Commission on the Reform of the Nomenclature of Organic Chemistry.²⁴

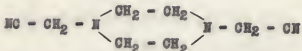
Typical structural formulae of compounds that appear in this dissertation are given below. In each case the official name accompanies the formula:



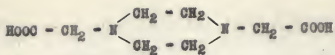
Piperasino-1,4-bis (alkyl acetate)



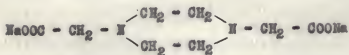
Piperasino-1,4-bis (ethanamide)



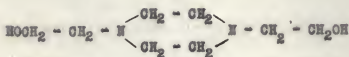
Piperasino-1,4-bis (ethanenitrile)



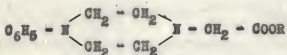
Piperazino-1,4-bis (acetic acid)



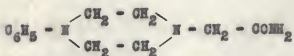
Piperazino-1,4-bis (sodium acetate)



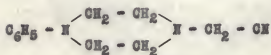
Piperazino-1,4-bis (beta-ethanol)



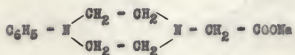
N-phenyl-piperazino-N'-alkyl acetate



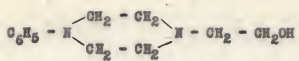
N-phenyl-piperazino-N'-ethanamide



N-phenyl-piperazino-N'-ethanenitrile



N-phenyl-piperazino-N'-sodium acetate



N-phenyl-piperazino-N' -beta-ethanol

DISCUSSION

One molecule of piperazine reacts with two molecules of alkyl chloroacetates to yield piperazino-1,4-bis (alkyl acetates). Two molecules of hydrogen chloride are split off in the reaction. The resulting ester has each of the imino groups of piperazine directly linked to the alpha-carbon atom of the alkyl acetate. The average yield is eighty to eighty-five per cent. This method of preparation has been used to synthesize a series of five esters where the alkyl groups are methyl, ethyl, n-propyl, n-butyl and n-hexyl.

Piperazino-1,4-bis (methyl acetate) and piperazino-1,4-bis (ethyl acetate) have been prepared before.^{5,6} The present method of preparation, however, represents an improvement in yield and method of purification and a saving of time. The boiling points of these compounds under reduced pressure, hitherto unknown, are reported in this dissertation.

In the piperazino-1,4-bis (alkyl acetate) series the methyl and ethyl derivatives are solids melting at 62.5° and 47.5° respectively. The n-propyl and n-butyl esters are oils and the n-hexyl ester is a solid that melts at 39.5° . Thus these amino esters are seen to have their melting points fall as one passes from methyl to the higher members of the series; in the case of the n-hexyl ester the melting point indicates that the curve in which melting point is plotted against the number of carbon atoms in the alkyl chain is beginning to rise. The boiling points of these esters increase from methyl to n-hexyl. The specific gravities and re-

fractive indexes of the liquid members bear the same relationships to each other that are normally encountered in series of esters. Three of these esters have been analysed as the di-acidsulfate, one as the free base and one as both the free base and the di-acidsulfate.

The piperazino-1,4-bis (alkyl acetates) are purified by distillation in vacuo or by means of the intermediate formation of the di-acidsulfate. In general, the former method is better.

Theoretically, still another method of purification of piperazino-1,4-bis (n-hexyl acetate) is possible. Since piperazine is water-soluble and piperazino-1,4-bis (n-hexyl acetate) is not, washing with water removes the former. The unchanged ester is then filtered off and dissolved in dilute hydrochloric acid. Extraction with ether removes any unchanged n-hexyl chloroacetate. Neutralization of the aqueous extract with dilute sodium hydroxide reprecipitates the free base, piperazino-1,4-bis (n-hexyl acetate). The low melting point (39.5°) of the latter, however, invariably leads at this stage to an oil which solidifies with extreme difficulty. Hence purification by means of the intermediate conversion into the di-acidsulfate of piperazino-1,4-bis (n-hexyl acetate) leads to optimum results and is adopted.

The preparation of piperazino-1,4-bis (ethanamide) and piperazino-1,4-bis (ethanenitrile) again represents an improvement over the methods previously reported^{5,6}. The yields obtained in the present method are quantitative. Piperazino-1,4-bis (ethanamide) arises from the elimination of two molecules of hydrogen chloride between the amino groups of one molecule of piperazine and the alpha-carbon atoms of two molecules of chloroethanamide. Piperazino-1,4-bis (ethanenitrile) arises in simi-

lar fashion from two molecules of chloroethanenitrile and one molecule of piperasine.

Piperasino-1,4-bis (ethanamide) can also be prepared from the action of cold, concentrated ammonium hydroxide on piperasino-1,4-bis (ethyl acetate). The yield is ninety per cent. The ease with which the amide is formed from the ester in this case does not seem to be as great as in the average case in which an ester is converted into an amide through the agency of ammonia. Piperasino-1,4-bis (ethyl acetate) requires a long interval of time for the transformation.

Acetic anhydride dehydrates piperasino-1,4-bis (ethanamide) to yield the corresponding di-nitrile, piperasino 1,4-bis (ethanenitrile). The dehydrating agent gives the best yields when used five times in excess of the theoretical quantity.

The preparation of piperasino-1,4-bis (acetic acid) as the di-acid sulfate through the agency of sodium nitrite and sulfuric acid takes place in quantitative yield. The yield and time involved in this method furnish a remarkable contrast to that reported by Van Dorp⁵ who attained the same result by refluxing piperasino-1,4-bis (ethanenitrile) with barium hydroxide. The fact that piperasino-1,4-bis (acetic acid) forms no ammonium salt enables the di-acidsulfate of piperasino-1,4-bis (acetic acid) to be converted into piperasino-1,4-bis (acetic acid) through the agency of concentrated ammonium hydroxide. It likewise permits in a single step the formation of piperasino-1,4-bis (acetic acid) from piperasino-1,4-bis (ethyl acetate). Refluxing the latter in ammonium hydroxide accomplishes the desired result.

Piperasino-1,4-bis (ethyl acetate) is reduced to piperasino-1,4-

bis (beta-ethanol) by means of sodium and n-butanol. The yield of the di-alcohol is severely affected by any deviation from the precautions enumerated in the Experimental Part of this dissertation. Piperazino-1,4-bis (beta-ethanol) obtained in this reduction is exactly the same as the piperazino-1,4-bis (beta-ethanol) produced by the action of ethylene oxide on piperazine in methanol solution²⁷.

The reduction of piperazino-1,4-bis (ethyl acetate) yields the corresponding alcohol in thirty per cent yield, the remainder of the ester appearing at the end of the reaction in the form of the sodium salt of the acid, piperazino-1,4-bis (sodium acetate). The latter possesses properties exactly analogous to those of piperazino-1,4-bis (sodium acetate) obtained by the elimination of two molecules of hydrogen chloride between one molecule of piperazine and two molecules of sodium chloroacetate²².

None of the compounds prepared in the N-phenyl-piperazine series have been synthesized before. As in the case of piperazine, N-phenyl-piperazine has been reacted with various derivatives of monochloroacetic acid, i.e., the esters, the nitrile, the amide and the sodium salt.

One molecule of N-phenyl-piperazine²³ reacts with one molecule of an alkyl chloroacetate to yield a N-phenyl-piperazino-N'-alkyl acetate. In the reaction a molecule of hydrogen chloride is eliminated between the free amino group of the base and the alpha-carbon atom of the alkyl chloroacetate. The yields vary from sixty to ninety per cent in the series. This method of preparation has been used to synthesize a series of four esters where the alkyl groups are methyl, ethyl, n-propyl and n-butyl.

In the N-phenyl-piperazino-N'-alkyl acetate series the first three members, methyl, ethyl and n-propyl, are liquids. N-phenyl-piper-

azino-N'-n-butyl acetate, however, is a solid that melts at 54-54.5°. This is a peculiarity seldom encountered. Usually the compound possessing the highest melting point in a series of esters is the methyl ester; as a rule, the higher esters melt lower than the methyl ester. N-phenyl-piperazino-N'-n-butyl acetate is a striking exception to this rule. The specific gravities of these esters decrease as one passes from methyl to n-propyl. This is normally found in a homologous series of esters. The refractive indexes decrease from the methyl to the n-propyl ester. This again is the normal behavior. The first three members of the series have been analyzed as the dihydrochlorides; N-phenyl-piperazino-N'-n-butyl acetate has been analyzed as the free base. N-phenyl-piperazino-N'-ethyl acetate has been analyzed both as the sulfate and the dihydrochloride.

The N-phenyl-piperazino-N'-alkyl acetates present a double problem in purification; first, the removal of N-phenyl-piperazino-N'-hydrochloride and second, the removal of N-phenyl-piperazine itself. Both of these substances are invariably present in small amounts as impurities in spite of the care with which the syntheses are effected. The former impurity is removed as a sticky solid by dissolving the ester in ether and filtering. The latter impurity is removed by distillation in vacuo. Removal of the N-phenyl-piperazino-N'-hydrochloride prior to distillation in vacuo enables the latter to be carried out more smoothly. When highly purified by distillation in vacuo the N-phenyl-piperazino-N'-alkyl acetates are odorless and light yellow in color; N-phenyl-piperazino-N'-n-butyl acetate, however, is a white solid.

N-phenyl-piperazino-N'-ethanamide is obtained by the elimination of hydrogen chloride between the free amino group of one molecule of N-

phenyl-piperazine²⁵ and the alpha-carbon atom of chloroethanamide^{16,17,18}. The yield is quantitative. The compound can also be prepared from the action of cold, concentrated ammonium hydroxide on N-phenyl-piperazino-N'-ethyl acetate. The yield is eighty-five per cent. This reaction proceeds more rapidly than does the corresponding conversion of piperazino-1,4-bis (ethyl acetate) into piperazino-1,4-bis (ethanamide).

N-phenyl-piperazino-N'-ethanenitrile arises from the elimination of one molecule of water from one molecule each of N-phenyl-piperazine, methanal and hydrogen cyanide. It is prepared in better yield, however, by the elimination of one molecule of hydrogen chloride from the free amino group of N-phenyl-piperazine and the methylene carbon atom of chloroethanenitrile. The compounds prepared by both methods are identical.

N-phenyl-piperazino-N'-ethyl acetate is reduced to N-phenyl-piperazino-N'-beta-ethanol by means of sodium and n-butanol. The yield is materially dependent on the degree to which the precautions listed in the Experimental Part of this dissertation are observed. N-phenyl-piperazino-N'-beta-ethanol obtained in this reduction is exactly the same as the N-phenyl-piperazino-N'-beta-ethanol produced by the elimination of one molecule of hydrogen chloride from one molecule of N-phenyl-piperazine²⁵ and one molecule of 2-chloro-ethanol²⁷.

The reduction of N-phenyl-piperazino-N'-ethyl acetate yields N-phenyl-piperazino-N'-beta-ethanol in thirty-five per cent yield. The remainder of the ester appears at the end of the reaction in the form of the sodium salt of the acid, N-phenyl-piperazino-N'-sodium acetate. The latter possesses properties analogous to those of N-phenyl-piperazino-N'-sodium acetate obtained by the elimination of one molecule of hydrogen chloride

between one molecule of N-phenyl-piperazine²³ and one molecule of sodium chloroacetate²².

The N-phenyl-piperazino-N'-alkyl acetates possess higher boiling points than the corresponding piperazino-1,4-bis (alkyl acetates). Data on the melting points are insufficient to warrant any comparison. The specific gravities and the refractive indexes of the N-phenyl-piperazino-N'-alkyl acetates are higher than those of the corresponding piperazino-1,4-bis (alkyl acetates). Both series of esters are characterized by solubility in the common organic solvents. The piperazino-1,4-bis (alkyl acetates) are soluble in water (piperazino-1,4-bis (n-hexyl acetate) is an exception); the N-phenyl-piperazino-N'-alkyl acetates are insoluble in water.

Piperazino-1,4-bis (ethanamide) melts at a higher temperature than N-phenyl-piperazino-N'-ethanamide. In like fashion piperazino-1,4-bis (ethanenitrile) melts at a higher temperature than N-phenyl-piperazino-N'-ethanenitrile. In both cases the solubilities of the N-phenyl-piperazino derivatives are greater and include a wider range of solvents than the piperazino derivatives.

In general, the reactivity in the N-phenyl-piperazine series of compounds is greater than that in the piperazine series. The purification of the liquid members of the N-phenyl-piperazine series is more difficult than in the case of the liquid members of the piperazine series. The solubilities of the compounds in the N-phenyl-piperazine series are without exception greater than those in the piperazine series.

n-Hexyl chloroacetate, hitherto unreported in the literature, has been synthesized and its physical constants listed.

The refractive indexes have been determined by means of an Abbe Refractometer with white light. Their accuracy is $\pm .001$. The specific gravities are accurate within $\pm .006$.

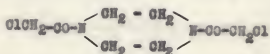
The remainder of this Discussion is inserted for the benefit of the reader who is not familiar with those phases of the field of organic chemistry with which this dissertation deals.

Piperazine itself is a remarkably stable body. In most reactions it behaves as a unit in which the piperazine ring remains intact. Hers³⁰ has heated piperazine with hydrochloric acid and sulfuric acid (separately) in a sealed tube at temperatures that range from 100° to 250°; in all cases, the piperazine ring is left intact. When administered orally or injected into the blood stream of mammals, the base may be recovered unchanged in the urine³³. Piperazine and many of its derivatives have been synthesized by ring closures involving 1,2-dichloro-ethane or 1,2-dibromo-ethane and primary amines^{1,31,32}. This indicates that the strength of the linkage between the carbon atoms of the piperazine ring should be of the same magnitude as that between the carbon atoms of a 1,2-disubstituted ethane compound. Bischoff³⁴ reports that the nitrogen-carbon linkage of 1,4-diphenyl piperazine is ruptured by means of hydrochloric acid and acetic acids. This indicates that the nitrogen-carbon linkage in the piperazine ring is less stable than the carbon-carbon linkage. More recent workers³⁵, however, have reported complete rupture of the nitrogen-carbon linkage in piperazine compounds. They conclude that the piperazine ring falls behind the following ring systems in the firmness of its structure: piperidine, pyrrolidine, dihydroindole, dihydroisoindole, morpholine and tetrahydroisoquinoline. None of the reactions re-

ported in this dissertation have been drastic enough to rupture the piperazine ring.

There are two possible ways in which piperazine and an alkyl chloroacetate can react in the presence of sodium carbonate in boiling ethanol (78°). The first involves the elimination of hydrogen chloride between the amino hydrogen atom and the chlorine atom attached to the alpha-carbon atom of the ester. The hydrogen chloride thus liberated reacts with the sodium carbonate to form sodium chloride (detected by the silver nitrate test), water and carbon dioxide (detected by virtue of the fact that the gas that escapes from the reaction mixture precipitates barium carbonate from a freshly filtered barium hydroxide solution).

The second possible way in which piperazine and an alkyl chloroacetate can react is with the elimination of two molecules of an alcohol between the ester group (-OR) of two molecules of the alkyl chloroacetate (ClCH_2COOR) and the two amino hydrogens of piperazine. This is purely hypothetical. First, cases of this type recorded in the literature call for sealed tube conditions (high pressures) and high temperatures. This reaction has been carried out in an open system at a moderate temperature. Second, the presence of sodium chloride and carbon dioxide as by-products of the reaction indicate that this second method of reaction does not take place. Third, if this second mode of reaction took place, 1,4-di (chloroacetyl) piperazine would be formed:



This compound has been synthesized by Abderhalden and Rossner²⁸ by the interaction of piperazine and chloroacetyl chloride. Neither its chemical properties, physical properties or analytical data agree with those of any piperazino-1,4-bis (alkyl acetate).

When one mol of piperazine and two mols of an alkyl chloroacetate react in the presence of an excess of sodium carbonate, the average yield of the piperazino-1,4-bis (alkyl acetate) thus formed is eighty to eighty-five per cent of theoretical. This fact and the absence of any unchanged alkyl chloroacetate at the end of the reaction supports the contention that the final product possesses a linkage involving one molecule of piperazine and two molecules of the ester. Quantitative analysis for nitrogen gives values that likewise preclude the possibility of the piperazino-1,4-bis (alkyl acetate) being a mono-substituted piperazine compound. For example, piperazino-1,4-bis (ethyl acetate) possesses 10.85% nitrogen and piperazino-1-ethyl acetate calls for 16.28% nitrogen. The average of three analytical determinations which do not differ from each other by more than four parts per thousand gives 10.69 as the percentage of nitrogen in the compound. Hence, analytical data support the argument for piperazino-1,4-bis (ethyl acetate) as the compound in question.

It is an accepted mode of procedure in organic chemistry to convert a compound whose structure is to be proven into a derivative and to compare all the properties of the latter with a sample of the derivative made by an independent method of synthesis. If complete agreement is found this is accepted as good evidence in support of the structure of the original compound. If now a series of such transformations and com-

parisons is made and all are found to be in agreement with each other and with theoretical expectations, the structure of the original compound is said to be definitely established. Such has been the method of attack followed in the work reported in this dissertation.

When piperasino-1,4-bis (ethyl acetate) reacts with ammonia, piperasino-1,4-bis (ethanamide) results. The latter is synthesized from piperasine, chloroethanamide and sodium carbonate. The chemical properties, physical properties and analytical results of the compounds made by these two methods are the same.

Piperasino-1,4-bis (ethyl acetate) is hydrolyzed to piperasino-1,4-bis (acetic acid) by refluxing in ammonium hydroxide solution. Piperasino-1,4-bis (acetic acid) is likewise formed by the action of ammonium hydroxide on the di-acidsulfate of piperasino-1,4-bis (acetic acid) which, in turn, is prepared by the action of sodium nitrite and sulfuric acid on piperasino-1,4-bis (ethanamide). This cycle may be represented as follows: piperasino-1,4-bis (ethyl acetate) $\rightarrow$ piperasino-1,4-bis (ethanamide) $\rightarrow$ di-acidsulfate of piperasino-1,4-bis (acetic acid) $\rightarrow$ piperasino-1,4-bis (acetic acid) $\leftarrow$ piperasino-1,4-bis (ethyl acetate). Comparison of analytical results, chemical properties and physical properties of these compounds indicates that the argument in question is further strengthened.

Piperasino-1,4-bis (ethanamide) produced from piperasino-1,4-bis (ethyl acetate) as indicated above yields piperasino-1,4-bis (ethanenitrile) upon dehydration with acetic anhydride. Piperasino-1,4-bis (ethanenitrile) thus formed is identical in chemical and physical properties with piperasino-1,4-bis (ethanenitrile) synthesized from piperasine,

chloroethanenitrile and sodium carbonate. A sample of each melts at 165° . A mixture of equal portions of each melts at 165° . It is an established fact that an intimate mixture in which the components are alike will have its melting point unchanged, whereas the mixing of two different compounds possessing the same melting point will usually, but not invariably, result in a different and usually a lower melting point. Although over three hundred thousand organic compounds are known fewer than twenty exceptions to this behavior have been reported^{36,37}. In light of this knowledge chances for error in the above reasoning are quite negligible.

Piperasino-1,4-bis (ethyl acetate) is reduced by means of sodium and n-butanol to piperasino-1,4-bis (beta ethanol). Piperasino-1,4-bis (sodium acetate) is a by-product of this reduction. The latter shows analogous analytical results and chemical and physical properties to piperasino-1,4-bis (sodium acetate) produced by the interaction of piperazine, sodium chloroacetate and sodium carbonate. The piperasino-1,4-bis (beta ethanol) produced in the reduction possesses similar chemical and physical properties to a sample²⁷ synthesized from piperazine and ethylene oxide in methanol solution. An intimate mixture of equal portions of the two samples melts at the same temperature as either component ($135-135.5^{\circ}$). Adelson, MacDowell and Pollard²⁷ have further characterized piperasino-1,4-bis (beta-ethanol) by conversion into the di-p-nitrobenzoate through the agency of p-nitrobenzoyl chloride and sodium hydroxide. These authors²⁷ have reduced the di-p-nitrobenzoate of piperasino-1,4-bis (beta-ethanol) to the di-p-aminobenzoate of piperasino-1,4-bis (beta-ethanol). Both compounds give analytical results that check with theoretical. This further strengthens the reasoning propounded in the preceding paragraphs.

In closing the question may arise as to why di-substituted piperazine compounds arise in preference to mono-substituted bodies. The recorded literature²⁹ supports this contention in view of the fact that both imino groups in the piperazine molecule are reported to have the same reaction velocity. The reactivity of the second imino group is reported to be enhanced after the first imino group has reacted²⁹. Moore, Boyle and Thorn³⁸ state that mono-substituted piperazine compounds arise if a definite p_H is maintained during the reaction. They conclude, on theoretical grounds, that if a proper p_H is maintained the following results when piperazine hydrochloride and ethyl chloroformate are allowed to react: ".....the hydrochloride of monocarbethoxy-piperazine forms. Even though the specific rate of reaction of ethyl chloroformate with monocarbethoxy-piperazine is so much greater than its rate of reaction with piperazine, the ratio of the concentration of monocarbethoxy-piperazine to that of piperazine hydrochloride is so small, and therefore so unfavorable to the former reaction, that a considerable quantity of the monocarbethoxy-piperazine should remain in solution as the hydrochloride." In sum, they postulate that, as the reaction proceeds, monocarbethoxy-piperazine is removed from the field of action as the hydrochloride and therefore the unreacted ethyl chloroformate unites with the piperazine hydrochloride. Jacobi²⁹ reports that he was unable to reproduce the results of Moore, Boyle and Thorn³⁸ at the hydrogen-ion concentration the latter recommend. He states that the nature of the substituting agents has no influence on the p_H at which mono-substitution occurs, but the differing ease with which they react makes it necessary to vary the conditions in order to obtain good yields. He duplicates the syntheses of the English authors³⁸ at a lower

Р_{II}. At all events, formation of mono-substituted piperazine compounds under the conditions described in this dissertation is not likely.

TABLE I

PHYSICAL CONSTANTS OF THE PIPERAZINO-1,4-BIS (ALKYL ACETATES)^a

Ester	M.P., °C. (corr.)	B.P., °C. (corr.)	Press., mm.	Bath, °C.	d ₂₀ ²⁰	n _D ²⁵
Methyl	62.5	156-157	5	210	--	--
Ethyl	47.5	158.5-159	4	200	--	--
n-Propyl	oil	177-178	5	220	1.052	1.461
n-Butyl	oil	194-194.5	4	230	1.022	1.447
n-Hexyl	39.5	228-230 ^b	5b	290	--	--

(a) average yield; 80-85%

(b) slight decomposition

TABLE II

ANALYSES OF THE PIPERAZINO-1,4-BIS (ALKYL ACETATES)

Ester	Analyses - %N			
	Free Base		Di-acidsulfate	
	calcd.	found	calcd.	found
Methyl	12.17	12.16		
Ethyl	10.85	10.69	6.17	6.12
n-Propyl			5.80	5.73
n-Butyl			5.49	5.41
n-Hexyl			4.95	5.02

TABLE III

PHYSICAL CONSTANTS OF THE N-PHENYL-PIPERAZINO-N'-ALKYL ACETATES

Ester	M.P., °C. (corr.)	B.P., °C. (corr.)	Press., mm.	Bath, °C.	d_{20}^{20}	n_D^{25}
Methyl	oil	175-177	4-5	245	1.121	1.549
Ethyl	oil	194-195	7-8	235	1.112	1.543
n-Propyl	oil	185-186	3-4	250	1.089	1.536
n-Butyl	54-54.5	218-220	8-9	270	--	--

TABLE IV

ANALYSES OF THE N-PHENYL-PIPERAZINO-N'-ALKYL ACETATES

Ester	Analyses - %N			
	Free Base calcd.	found	Dihydrochloride calcd.	found
Methyl			9.12	9.09
Ethyl	8.09 ^a	8.09 ^a	8.72	8.56
n-Propyl			8.36	8.43
n-Butyl	10.14	10.02		

(a) sulfate

PREPARATION OF INTERMEDIATES

1. Ethyl Chloroacetate^{10,11}

200 grams of monochloroacetic acid, 120 grams of ethanol and 25 grams of concentrated sulfuric acid are warmed on the water bath for six hours. After cooling, the solution is poured into an excess of sodium carbonate solution and then extracted with ether. The ethereal solution is dried over anhydrous sodium sulfate. Fractionation yields a colorless liquid which boils at 144-145°.

2. Methyl Chloroacetate^{10,12}

This is obtained in the usual fashion by saturating a solution of monochloroacetic acid in excess methanol with dry hydrogen chloride gas. The ester boils at 130°.

3. n-Propyl Chloroacetate^{13,14}

n-Propyl chloroacetate is synthesized exactly as is ethyl chloroacetate, 160 grams of n-propanol being used in place of 120 grams of ethanol. The ester boils at 161-162°.

4. n-Butyl Chloroacetate^{13,15}

n-Butyl chloroacetate is prepared under the same conditions as ethyl chloroacetate from 200 grams of monochloroacetic acid, 195 grams of n-butanol and 25 grams of concentrated sulfuric acid. The pure ester boils at 175°.

5. n-Hexyl Chloroacetate

This ester has not previously been prepared. Its preparation and properties are discussed under the experimental portion of this dissertation.

16,17,18,21

6. Chloroethanamide

215 grams of ethyl chloroacetate are cooled to 0° and 200 cc. of chilled, concentrated ammonium hydroxide are added. The solution is stirred in the cold for fifteen minutes; then another 200 cc. portion of ammonium hydroxide is added and the stirring is continued for fifteen minutes. After standing for thirty minutes the crystals of chloroethanamide (yield, eighty per cent) are filtered and recrystallized from water. The recrystallized product melts at $119-120^{\circ}$.

17,19,20

7. Chloroethanenitrile

Chloroethanamide is heated with an excess of phosphorus pentoxide, the fuming liquid (chloroethanenitrile) which boils over being caught in a receiver. Inasmuch as some chloroethanamide sublimes and is swept over with the desired product, the latter must be further purified. This is accomplished by refluxing for one hour over a fresh portion of phosphorus pentoxide followed by careful distillation. Pure chloroethanenitrile boils at $123-124^{\circ}$.

8. Sodium Chloroacetate^{22,26}

Equivalent quantities of monochloroacetic acid and sodium hydroxide, each dissolved in ethanol, are mixed. White, pearly crystals of sodium chloroacetate precipitate out.

9. N-Phenyl-piperazine²³

Aniline and diethanolamine are mixed in molar proportions and concentrated hydrochloric acid is added until the solution is neutral to litmus. The water is then boiled off and when the temperature has reached 220 to 240° it is kept there for six hours. After cooling, concentrated sodium hydroxide is added to liberate the free base which is fractionated

146-8⁰
in vacuo. Boiling point, 155-157⁰ at 10 mm.

10. Anhydrous Piperazine⁴

Piperazine hexahydrate is placed in a vacuum desiccator over solid potassium hydroxide. After standing in vacuo for a week, the piperazine is anhydrous and ready for use.

All other chemicals and reagents employed in this investigation have been obtained from commercial sources. Many of them, however, have been subjected to further purification before use.

EXPERIMENTAL

Piperazino-1,4-bis (ethyl acetate)

19.4 grams (0.1 mol) of piperazine hexahydrate (or 8.6 grams of anhydrous piperazine⁴), 24.5 grams (0.2 mol) of ethyl chloroacetate^{10,11} and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of 95% ethanol. The suspension is refluxed for two hours on the water bath. Filtration followed by evaporation of the ethanol yields an oil, piperazino-1,4-bis (ethyl acetate), which solidifies upon cooling with ice. The ester may be purified by distillation in vacuo. The physical constants of the highly purified ester are given below:

b.p. °C., corr.	Press., mm.	Bath, °C.
158.5-159	4	200
177-178	5-6	220
182-183	9	220

Piperazino-1,4-bis (ethyl acetate) melts at 47.5°. It is soluble in water and the common organic solvents. Analyses of this compound and subsequent conversion into piperazino-1,4-bis (ethanamide), which is identical with a sample made by an independent synthesis, corroborate the assigned structure.

Calculated for $C_{12}H_{22}O_4N_2$: N, 10.85. Found: N, 10.69

An alternative method of purification of piperazino-1,4-bis (ethyl acetate) is outlined below.

Di-acidsulfate of piperazino-1,4-bis (ethyl acetate)

25.8 grams (0.1 mol) of piperazino-1,4-bis (ethyl acetate) are

dissolved in 250 cc. of ether and the resulting solution is cooled in an ice bath. Cold, concentrated sulfuric acid is then added with stirring until a white precipitate is no longer formed. The di-acidsulfate of piperazino-1,4-bis (ethyl acetate) is filtered from the ether solution, washed with several portions of cold ether in order to remove the excess sulfuric acid and is placed between porous plates to dry. The yield is quantitative. This compound is very soluble in water and insoluble in the common organic solvents. It is purified by repeated crystallizations from 95% ethanol from which it crystallizes in long, white needles. Prior to analysis it is dried in vacuo over solid potassium hydroxide.

Calculated for $C_{12}H_{22}O_4N_2 \cdot 2H_2SO_4$: N, 6.17. Found: N, 6.12.

45.4 grams (0.1 mol) of the di-acidsulfate of piperazino-1,4-bis (ethyl acetate) are suspended in 400 cc. of ether and the suspension is cooled in an ice bath. 10 cc. of water and 31.8 grams (0.3 mol) of sodium carbonate are added and the suspension is thoroughly stirred for fifteen minutes, at the end of which time the evolution of CO_2 is complete. The ethereal solution is filtered and dried over anhydrous sodium carbonate. Filtration and evaporation of the ether leaves white crystals of piperazino-1,4-bis (ethyl acetate) which melt at 47.5° . The yield is eighty per cent, based on the pure di-acidsulfate of piperazino-1,4-bis (ethyl acetate).

The most satisfactory method of purifying piperazino-1,4-bis (ethyl acetate) is by distillation in vacuo. The average yield of this ester and other piperazino-1,4-bis (alkyl acetates) purified in this fashion is eighty to eighty-five per cent (based on piperazine).

Piperazino-1,4-bis (methyl acetate)

19.4 grams (0.1 mol) of piperazine hexahydrate (or 8.6 grams of anhydrous piperazine), 21.7 grams (0.2 mol) of methyl chloroacetate^{10,12} and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of 95% ethanol. The suspension is refluxed for two hours on a water bath. Filtration followed by evaporation of the ethanol yields an oil, piperazino-1,4-bis (methyl acetate), which solidifies on cooling. The ester may be purified by distillation in vacuo. It boils at 156-157° at 5 mm. (bath temperature, 210°). It is extremely soluble in water and the common organic solvents. Piperazino-1,4-bis (methyl acetate), when highly purified, melts at 62.5°.

An alternative method of purification lies in the formation of the di-acidsulfate and subsequent reconversion into the free base.

23.0 grams (0.1 mol) of piperazino-1,4-bis (methyl acetate) are dissolved in 250 cc. of ether and the resulting solution is cooled in an ice bath. Cold, concentrated sulfuric acid is then added with stirring until a white precipitate is no longer formed. The di-acidsulfate of piperazino-1,4-bis (methyl acetate) is filtered from the ether, washed with several portions of cold ether and placed between porous plates to dry. It is very soluble in water and insoluble in the common organic solvents. Inasmuch as the di-acidsulfate of piperazino-1,4-bis (methyl acetate) cannot be satisfactorily recrystallized, it has not been analyzed. It has been washed repeatedly with ethanol and ether before reconversion to the free base.

42.6 grams (0.1 mol) of the di-acidsulfate of piperazino-1,4-bis (methyl acetate) are suspended in 400 cc. of ether which is cooled in

an ice bath. 10 cc. of water and 31.8 grams (0.1 mol) of sodium carbonate are added and the cold suspension is stirred thoroughly until no further evolution of CO_2 takes place (about fifteen minutes). The ethereal solution is filtered and dried over sodium carbonate. Filtration and evaporation of the ether leaves white crystals of piperazino-1,4-bis (methyl acetate) which melt at 62.5° . The yield is seventy-five per cent, based on the crude di-acidsulfate of piperazino-1,4-bis (methyl acetate).

Purification is most satisfactorily effected by distillation in vacuo. The average yield of the ester is eighty to eighty-five per cent.

Analyses of piperazino-1,4-bis (methyl acetate): Calculated for $\text{C}_{10}\text{H}_{18}\text{O}_4\text{N}_2$: N, 12.17. Found: N, 12.18.

Piperazino-1,4-bis (n-propyl acetate)

19.4 grams (0.1 mol) of piperazine hexahydrate, 27.3 grams (0.2 mol) of n-propyl chloroacetate^{13,14} and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of 95% ethanol. The suspension is refluxed for two hours on the water bath. Filtration followed by evaporation of the ethanol yields an oil, piperazino-1,4-bis (n-propyl acetate), which does not solidify when cooled in an ice-salt mixture. The ester may be purified by distillation in vacuo.

Piperazino-1,4-bis (n-propyl acetate) is a colorless, odorless oil, soluble in water and the common organic solvents. The purified ester boils at $177-178^\circ$ at 5 mm. (bath temperature, 220°). Its specific gravity at 20° (referred to water at 20°) is 1.052. At 25° it possesses a refractive index equal to 1.461 (Abbé Refractometer).

For purposes of analysis the di-acidsulfate of piperazino-1,4-bis (n-propyl acetate) has been prepared.

Di-acidsulfate of Piperazino-1,4-bis (n-propyl acetate)

28.6 grams (0.1 mol) of piperazino-1,4-bis (n-propyl acetate) are dissolved in 250 cc. of ether and the resulting solution is cooled in an ice bath. Cold, concentrated sulfuric acid is then added with stirring until the formation of a white precipitate is complete. The di-acidsulfate of piperazino-1,4-bis (n-propyl acetate) is separated from the ethereal solution by filtration, washed with several portions of cold ether and placed between porous plates to dry. The yield is quantitative. The di-acidsulfate of piperazino-1,4-bis (n-propyl acetate) is soluble in water and insoluble in the common organic solvents. It is purified by repeated crystallisations from 95% ethanol. It is dried in vacuo over solid potassium hydroxide prior to analysis.

Calculated for $C_{14}H_{26}O_4N_2 \cdot 2H_2SO_4$: N, 5.80. Found: N, 5.73.

48.2 grams (0.1 mol) of the di-acidsulfate of piperazino-1,4-bis (n-propyl acetate) are suspended in 400 cc. of ether which is cooled in an ice bath. 10 cc. of water and 31.8 grams (0.3 mol) of sodium carbonate are added and the suspension is thoroughly stirred for fifteen minutes. The ethereal solution is filtered and dried over anhydrous sodium carbonate. Filtration and evaporation of the ether leaves a colorless oil, piperazino-1,4-bis (n-propyl acetate).

In this case distillation in vacuo is also the best procedure for purifying the ester. The average yield is eighty per cent.

Piperasino-1,4-bis (n-butyl acetate)

19.4 grams (0.1 mol) of piperasine hexahydrate, 30.1 grams (0.2 mol) of n-butyl chloroacetate^{13,15} and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of 95% ethanol. The suspension is refluxed for two hours on the water bath. Filtration followed by evaporation of the ethanol yields an oil, piperasino-1,4-bis (n-butyl acetate), which does not solidify when cooled in an ice-salt mixture. The compound may be purified by distillation in vacuo.

Piperasino-1,4-bis (n-butyl acetate) is a colorless, odorless oil that is soluble in water and the common organic solvents. The pure ester boils at $194-4.5^{\circ}$ at 4 mm. (bath temperature, 230°) and possesses a specific gravity at 20° of 1.022 (referred to water at 20°). Its refractive index at 25° is 1.447 (Abbé Refractometer).

For purposes of analysis, the di-acidsulfate of piperasino-1,4-bis (n-butyl acetate) has been prepared.

Di-acidsulfate of Piperasino-1,4-bis (n-butyl acetate)

31.4 grams (0.1 mol) of piperasino-1,4-bis (n-butyl acetate) are dissolved in 250 cc. of ether and the resulting solution is cooled in an ice bath. Cold, concentrated sulfuric acid is then added with stirring until a white precipitate is no longer formed. The di-acidsulfate of piperasino-1,4-bis (n-butyl acetate) is filtered from the ether solution, washed with several portions of cold ether and placed between porous plates to dry. The yield is quantitative. The compound is very soluble in water, soluble in methanol, soluble in hot ethanol and n-butanol and insoluble in cold ethanol and n-butanol. It is best purified by repeated

recrystallizations from 95% ethanol. Prior to analysis it is dried in vacuo over solid potassium hydroxide.

Calculated for $C_{16}H_{30}O_4N_2 \cdot 2H_2SO_4$: N, 5.49. Found: N, 5.41.

51.0 grams (0.1 mol) of the di-acidsulfate of piperasino-1,4-bis (n-butyl acetate) are suspended in 400 cc. of ether which is cooled in an ice bath. 10 cc. of water and 31.8 grams (0.3 mol) of sodium carbonate are added and the suspension is thoroughly stirred until evolution of CO_2 is complete (about fifteen minutes). The ethereal solution is filtered and dried over anhydrous sodium carbonate. Filtration and evaporation of the ether leaves a colorless oil, piperasino-1,4-bis (n-butyl acetate), in eighty per cent yield, based on the pure di-acidsulfate of piperasino-1,4-bis (n-butyl acetate).

Purification is best effected, however, by distillation in vacuo.

Piperasino-1,4-bis (n-hexyl acetate)

19.4 grams (0.1 mol) of piperasine hexahydrate, 35.7 grams (0.2 mol) of n-hexyl chloroacetate and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of 95% ethanol. The suspension is refluxed for two hours on the water bath. Filtration followed by evaporation of the ethanol leaves an oil, piperasino-1,4-bis (n-hexyl acetate), which solidifies upon cooling in an ice bath. The compound may be purified by distillation in vacuo, although this process is here accompanied by slight decomposition.

Piperasino-1,4-bis (n-hexyl acetate) is a white crystalline solid which melts at 39.5° . It is insoluble in water but soluble in the common organic solvents. It boils with slight decomposition at $228-230^\circ$ at 5 mm.

(bath temperature = 290°).

Piperasino-1,4-bis (n-hexyl acetate) has been analyzed as the di-acidsulfate.

Di-acidsulfate of Piperasino-1,4-bis (n-hexyl acetate)

37.0 grams (0.1 mol) of piperasino-1,4-bis (n-hexyl acetate) are dissolved in 250 cc. of ether and the resulting solution is cooled in an ice bath. Cold, concentrated sulfuric acid is then added with stirring until a white precipitate is no longer formed. The di-acidsulfate of piperasino-1,4-bis (n-hexyl acetate) is filtered from the ether solution, washed with several portions of cold ether and placed between porous plates to dry. The yield is quantitative. This compound is soluble in water and insoluble in the common organic solvents. It is purified by recrystallization from absolute ethanol. Prior to analysis it is dried in vacuo over solid potassium hydroxide.

Calculated for $C_{20}H_{38}O_4N_2 \cdot 2H_2SO_4$: N, 4.95. Found: N, 5.02.

56.6 grams (0.1 mol) of the di-acidsulfate of piperasino-1,4-bis (n-hexyl acetate) are suspended in 400 cc. of ether which is cooled in an ice bath. 10 cc. of water and 31.8 grams (0.3 mol) of sodium carbonate are added and the solution is stirred thoroughly until the evolution of CO_2 is complete (about fifteen minutes). The ethereal solution is filtered and dried over anhydrous sodium carbonate. Filtration and evaporation of the ether leaves white crystals of piperasino-1,4-bis (n-hexyl acetate) which melt at 39.5° . The yield is eighty per cent, based on the pure di-acidsulfate of piperasino-1,4-bis (n-hexyl acetate).

Inasmuch as distillation in vacuo of piperasino-1,4-bis (n-hexyl

acetate) is attended by slight decomposition, purification is most effectively accomplished through the agency of intermediate formation of the di-acidsulfate.

n-Hexyl Chloroacetate

91 grams of hexanol are placed in a flask and 120 grams of chloroacetyl chloride are added, the flask being cooled externally. Hydrogen chloride is copiously evolved and much heat is developed. The solution is refluxed on an oil bath at 150° for three hours, cooled and poured into an excess of sodium carbonate solution. The alkaline solution is extracted with ether and the ethereal solution is dried over anhydrous sodium sulfate. Filtration of the ether solution followed by evaporation of the solvent leaves n-hexyl-chloroacetate. The latter is purified by distillation at atmospheric pressure through an efficient column that is wrapped in asbestos.

n-Hexyl chloroacetate is a colorless liquid that possesses a distinct fruity odor. It boils at $218.5-219.5^{\circ}$ at 758 mm. and has a specific gravity of 1.026 at 20° (referred to water at 20°). At 25° it has a refractive index of 1.435 (Abbé Refractometer).

n-Hexyl chloroacetate has been analysed as the di-acidsulfate of piperasino-1,4-bis (n-hexyl acetate). Calculated for $C_{20}H_{38}O_4N_2 \cdot 2H_2SO_4$: N, 4.95. Found: N, 5.02.

Piperasino-1,4-bis (ethanamide)

19.4 grams (0.1 mol) of piperazine hexahydrate, 19.7 grams (0.2 mol) of chloroethanamide^{16,17,18,21} and 15.9 grams (0.15 mol) of sodium

carbonate are suspended in 100 cc. of toluene and refluxed on an oil bath for two hours. After cooling and filtering, the solid residue is washed with a small amount of ether (to remove the last traces of toluene) and extracted with hot water. The desired product crystallizes from the latter in ninety per cent yield. The compound chars over 250° . It is soluble in hot water, insoluble in cold water and insoluble (cold) in the common organic solvents.

Calculated for $C_8H_{16}O_2N_4$: N, 27.99. Found: N, 27.87.

Conversion of Piperazino-1,4-bis (ethyl acetate) into Piperazino-1,4-bis (ethanamide)

Piperazino-1,4-bis (ethyl acetate) is converted into piperazino-1,4-bis (ethanamide) through the agency of either alcoholic ammonia or concentrated ammonium hydroxide. The latter method gives a higher yield of a purer product.

4.5 grams of piperazino-1,4-bis (ethyl acetate) are dissolved in 40 cc. of anhydrous alcoholic ammonia and the resulting solution is placed in a tight-fitting, glass-stoppered bottle of 40 cc. capacity. After two weeks precipitation of piperazino-1,4-bis (ethanamide) is complete. The yield is sixty per cent. The compound is recrystallized from water prior to analysis. It chars over 250° ; a mixed melting point determination with an authentic specimen behaves similarly.

Calculated for $C_8H_{16}O_2N_4$: N, 27.99. Found: N, 28.12.

3 grams of piperazino-1,4-bis (ethyl acetate) are placed in a glass-stoppered bottle of 25 cc. capacity and the latter is then filled with concentrated ammonium hydroxide. The bottle is shaken until solution

is complete (about three minutes). After standing for forty-eight hours in the ice box precipitation of piperasino-1,4-bis (ethanamide) is complete. The yield is ninety per cent. The compound is recrystallized from water. It chars over 250° ; a mixed melting point determination with an authentic specimen of piperasino-1,4-bis (ethanamide) behaves similarly.

Calculated for $C_8H_{16}O_2N_4$: N, 27.99. Found: N, 27.90.

Piperasino-1,4-bis (ethanenitrile)

19.4 grams (0.1 mol) of piperasine hexahydrate, 15.1 grams (0.2 mol) of chloroethanenitrile^{17,19, 20} and 15.9 grams (0.15 mol) of sodium carbonate are suspended in 100 cc. of toluene. The resulting suspension is refluxed on the oil bath for two hours. After cooling the solids are filtered off, the filtrate discarded and the residue is washed with a small amount of isopropyl ether to remove the last traces of toluene. The solid material is then agitated with 50 cc. of cold water to remove the inorganic salts and the insoluble piperasino-1,4-bis (ethanenitrile) is recovered by filtration. The yield is sixteen grams, ninety-nine per cent of theoretical.

Piperasino-1,4-bis (ethanenitrile) is insoluble in cold water and toluene and only slightly soluble in ether, ethanol and isopropyl ether. Repeated crystallizations from 95% ethanol give highly purified crystals which melt at 165° .

Calculated for $C_8H_{12}N_4$: N, 34.14. Found: N, 33.98.

Conversion of Piperazino-1,4-bis (ethanamide) into Piperazino-1,4-bis
(ethanenitrile)

10 grams (0.05 mol) of piperazino-1,4-bis (ethanamide) are pulverized and dropped into 51 grams (0.5 mol) of acetic anhydride which are contained in a small flask. The solution is refluxed for one hour, cooled and poured onto cracked ice. The resulting solution is made alkaline with sodium carbonate and repeatedly extracted with isopropyl ether. The latter is dried over sodium carbonate, filtered and evaporated. Recrystallization of the residue from 95% ethanol gives crystals which melt at 165°. The yield is thirty-five per cent. A mixed melting point determination with an authentic specimen of piperazino-1,4-bis (ethanenitrile) shows no depression.

Di-acidsulfate of Piperazino-1,4-bis (acetic acid)

10 grams of pulverized piperazino-1,4-bis (ethanamide) are dissolved in 150 grams of concentrated sulfuric acid aided by gently warming on the water bath and a cold, saturated solution of sodium nitrite (10 grams) is slowly added by means of a dropping funnel, the lower end of which is kept near the bottom of the sulfuric acid solution. The beaker containing the reaction solution is placed in a water bath and the latter is slowly heated to the boiling point where it is maintained for three to four minutes. Nitrogen is evolved profusely. 100 grams of ice are added to the cooled solution; after one hour precipitation of the di-acidsulfate of piperazino-1,4-bis (acetic acid) is complete. The yield of the hygroscopic white powder is quantitative. It is recrystallized from dilute sulfuric acid (1:4 by volume) and oven dried. The compound is dried over

solid potassium hydroxide in vacuo prior to analysis.

Calculated for $C_8H_{14}O_4N_2 \cdot 2H_2SO_4$: N, 7.03. Found: N, 6.86.

Piperasino-1,4-bis (acetic acid)

4 grams (0.01 mol) of the di-acidsulfate of piperasino-1,4-bis (acetic acid) are dissolved in 25 cc. of concentrated ammonium hydroxide and the resulting solution is evaporated to a small volume. Piperasino-1,4-bis (acetic acid) crystallizes out in eighty per cent yield. The compound crystallizes from water with two molecules of water of crystallization and decomposes over 250° . It is insoluble in the common organic solvents. An aqueous solution of piperasino-1,4-bis (acetic acid) is distinctly acid to litmus, yet the compound forms no ammonium salt. The compound is dried in vacuo over phosphorus pentoxide prior to analysis.

Calculated for $C_8H_{14}O_4N_2 \cdot 2H_2O$: N, 11.76; H_2O , 15.13.

Found: N, 11.96; H_2O , 15.12.

The di-hydrate of piperasino-1,4-bis (acetic acid) is dried in an oven at 105° for four hours and analysed. Calculated for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.96.

Piperasino-1,4-bis (acetic acid) is also formed by refluxing piperasino-1,4-bis (ethyl acetate) in ammonium hydroxide solution. 12.9 grams (0.05 mol) of piperasino-1,4-bis (ethyl acetate) are refluxed in 200 cc. of ammonium hydroxide for two hours. The ammoniacal solution is evaporated to a small volume, whereupon crystals of the di-hydrate of piperasino-1,4-bis (acetic acid) separate. The yield is fifty per cent. The compound decomposes over 250° and is found to be identical with a specimen prepared by the action of nitrous acid on piperasino-1,4-bis (ethanamide).

Reduction of piperasino-1,4-bis (ethyl acetate)

Piperasino-1,4-bis (ethyl acetate) is purified for this reaction by distillation in vacuo and is then placed in vacuo over phosphorus pentoxide for at least twenty-four hours prior to use. The n-butanol is obtained anhydrous just prior to use by fractional distillation through an efficient column; the first one hundred cc. of the distillate are rejected and the fraction boiling at $117-118^{\circ}$ is collected.

The reaction is carried out in a two-neck flask to which is attached a long, water-cooled condenser. The top of the latter is fitted with a calcium chloride tube.

It is absolutely essential that the above precautions be observed. Failure to use reagents of high purity and anhydrous media causes the yields to be cut severely.

25.8 grams (0.1 mol) of piperasino-1,4-bis (ethyl acetate) are dissolved in 400 cc. of freshly-distilled n-butanol and the solution is poured into a two-neck flask of liter capacity to which has been fitted a long, water-cooled condenser as indicated above. 28 grams (1.2 mols) of sodium cut in large chunks (about seven pieces, each the size of one's thumb) are dropped in rapidly. The flask is surrounded by an ice-bath until the initial vigorous reaction has subsided; the freezing mixture is then removed and the reaction is allowed to proceed without external cooling. The flask is heated on an oil bath (bath temperature, 150°) until all of the sodium has disappeared (average time, three hours), care being taken to maintain anhydrous conditions throughout. After cooling somewhat, 100 cc. of water are added and all of the n-butanol is removed by rapid steam distillation. The strongly alkaline solution (volume, 100 cc.)

that remains in the flask is now repeatedly extracted with hot amyl acetate. The latter is separated while hot and distilled until only a small volume remains. This is boiled with norite and filtered. Piperasino-1,4-bis (beta-ethanol) crystallizes from the filtrate. The yield is thirty per cent. Repeated crystallizations from amyl acetate yield crystals which melt at $135-135.5^{\circ}$. A mixed melting point determination with an authentic specimen²⁷ of piperasino-1,4-bis (beta-ethanol) shows no depression.

Piperasino-1,4-bis (sodium acetate)

After the concentrated alkaline solution resulting from the reduction of piperasino-1,4-bis (ethyl acetate) has been repeatedly extracted with hot amyl acetate, it is cooled and the solid that forms is filtered. The residue is boiled with an alcohol-water mixture, (4:1 by volume), and norite and filtered. Silky needles of piperasino-1,4-bis (sodium acetate) crystalline out upon cooling. They are very soluble in water, insoluble in the common organic solvents and are best recrystallized from an ethanol-water mixture of the above composition. Piperasino-1,4-bis (sodium acetate) is dried in an oven at 105° for four hours prior to analysis.

Calculated for $C_8H_{12}O_4N_2Na_2$: N, 11.38. Found: N, 11.43.

5.6 grams (0.1 mol) of anhydrous piperasine⁴, 23.3 grams (0.2 mol) of sodium chloroacetate^{22,26} and 15.9 grams (0.15 mol) of sodium carbonate are refluxed in 100 cc. of xylene in an oil bath for one hour. After cooling the solids are filtered and washed with ether to remove the last traces of xylene. Piperasino-1,4-bis (sodium acetate) is purified by crystallization from ethanol-water mixture (4:1, by volume) and is identical in all of its properties to the compound obtained as a by-product in the reduction of

piperasino-1,4-bis (ethyl acetate).

Calculated for $C_{18}H_{24}O_4N_2Na$: N, 11.38. Found: N, 11.40.

N-Phenyl-piperasino-N'-ethyl acetate

32.4 grams (0.2 mol) of N-phenyl-piperasine, 31.8 grams (0.3 mol) of sodium carbonate and 24.5 grams (0.2 mol) of ethyl chloroacetate^{10,11} are suspended in 100 cc. of 95% ethanol. The suspension is refluxed vigorously on a water bath for two hours and filtered. The ethanol is evaporated on a steam bath. After cooling the yellow oil that remains is treated with ether. Most of the crude oil dissolves leaving a small amount of a sticky solid which is some N-phenyl-piperasino-N'-hydrochloride that is invariably formed in the synthesis in spite of the excess of sodium carbonate. Removal of this small amount of solid matter at this point is very desirable because it allows subsequent distillation in vacuo of the desired product to be conducted more smoothly and with a minimum amount of bumping. The same procedure is followed to advantage with all of the N-phenyl-piperasino-N'-alkyl acetates. The ether solution is filtered from the small amount of solid matter and is evaporated in a current of air until only a yellow oil remains. The latter is purified by distillation in vacuo. The average yield is eighty to ninety per cent of theoretical.

N-phenyl-piperasino-N'-ethyl acetate boils at 213-214° at 9-10 mm. (bath temperature, 245°) and at 194-195° at 7-8 mm. (bath temperature, 235°). Its specific gravity at 20° (referred to water at 20°) is 1.112. At 25° it possesses a refractive index equal to 1.543 (Abbé Refractometer). N-phenyl-piperasino-N'-ethyl acetate is a very light yellow oil that is insoluble in water and soluble in the common organic solvents.

It has been converted into the di-hydrochloride of N-phenyl-piperasino-N'-ethyl acetate and into the sulfate of N-phenyl-piperasino-N'-ethyl acetate for analytical purposes.

Di-hydrochloride of N-phenyl-piperasino-N'-ethyl acetate

9.5 grams of vacuo-distilled N-phenyl-piperasino-N'-ethyl acetate are dissolved in 150 cc. of ether and anhydrous hydrogen chloride gas is bubbled in. After twenty minutes precipitation of the solid di-hydrochloride of N-phenyl-piperasino-N'-ethyl acetate is complete. The yield is ninety per cent (10.8 grams).

The di-hydrochloride of N-phenyl-piperasino-N'-ethyl acetate is soluble in water, 95% ethanol and n-butanol and insoluble in ethyl acetate. Successive crystallizations from 95% ethanol yield white crystals that are suitable for analysis. The compound is very hygroscopic.

Calculated for $C_{14}H_{20}O_2N_2 \cdot 2HCl$: N, 8.72. Found: N, 8.56.

Sulfate of N-phenyl-piperasino-N'-ethyl acetate

7 grams of vacuo-distilled N-phenyl-piperasino-N'-ethyl acetate are dissolved in 150 cc. of ether and the solution is cooled in an ice bath. Cold, concentrated sulfuric acid is added with stirring until precipitation of the sulfate of N-phenyl-piperasino-N'-ethyl acetate is complete. The latter is filtered off, washed with several portions of ether and dried between porous plates. The yield is quantitative (10 grams).

The sulfate of N-phenyl-piperasino-N'-ethyl acetate is prepared for analysis by recrystallization from 95% ethanol.

Calculated for $C_{14}H_{20}O_4N_2 \cdot H_2SO_4$: N, 8.09. Found: N, 8.09.

N-Phenyl-piperasino-N'-methyl acetate

16.2 grams (0.1 mol) of N-phenyl-piperazine²³, 15.9 grams (0.15 mol) of sodium carbonate and 10.9 grams (0.1 mol) of methyl chloroacetate^{10,12} are suspended in 100 cc. of 95% ethanol. The suspension is refluxed vigorously on the water bath for two hours and filtered. Evaporation of the ethanol leaves a yellow oil to which, after cooling, ether is added with stirring. The ethereal solution is filtered from the small amount of sticky solid that forms and is evaporated in a current of air. The yellow oil that remains, crude N-phenyl-piperasino-N'-methyl acetate, is purified by distillation in vacuo. The yield is seventy to seventy-five per cent.

N-phenyl-piperasino-N'-methyl acetate boils at 175-177° at 4-5 mm. (bath temperature, 245°). It is a very pale yellow oil that possesses at 20° a specific gravity of 1.121 (referred to water at 20°). Its refractive index at 25° is 1.548 (Abbé Refractometer). N-phenyl-piperasino-N'-methyl acetate is insoluble in water and soluble in the common organic solvents.

This ester has been analyzed as the di-hydrochloride.

Di-hydrochloride of N-phenyl-piperasino-N'-methyl acetate

9 grams of vacuo-distilled N-phenyl-piperasino-N'-methyl acetate are dissolved in 150 cc. of ether and anhydrous hydrogen chloride gas is bubbled in until precipitation is complete. The yield is ninety per cent.

The di-hydrochloride of N-phenyl-piperasino-N'-methyl acetate is soluble in water and ethanol. It is purified by repeated crystallizations from n-butanol. Prior to analysis it is dried in an oven at 105° for six

hours.

Calculated for $C_{13}H_{18}O_2N_2 \cdot 2HCl$: N, 9.12. Found: N, 9.09.

N-Phenyl-piperasino-N'-n-propyl acetate

32.4 grams (0.2 mol) of N-phenyl-piperasine²³, 31.8 grams (0.3 mol) of sodium carbonate and 27.4 grams (0.2 mol) of n-propyl chloroacetate^{13,14} are suspended in 100 cc. of 95% ethanol. The resulting suspension is refluxed vigorously on the water bath for two hours and filtered. The ethanol is evaporated and the resulting yellow oil is cooled; ether is added with stirring. The ethereal solution is filtered from a small amount of sticky solid matter and placed in a current of air until all of the ether is evaporated. The yellow oil that remains, crude N-phenyl-piperasino-N'-n-propyl acetate, is purified by distillation *in vacuo*. The yield is sixty to sixty-five per cent.

N-phenyl-piperasino-N'-n-propyl acetate distills in *vacuo* under the following conditions:

b.p. °C., corr.	Pressure	Bath temp.
185-186	3-4 mm.	250°
197-198	5 mm.	280°
210-211	8-10 mm.	270°

At 20° it has a specific gravity of 1.089 (referred to water at 20°). It has a refractive index equal to 1.536 at 25° (Abbe Refractometer). N-phenyl-piperasino-N'-n-propyl acetate is a very light yellow oil that is insoluble in water and soluble in the common organic solvents.

The ester has been analysed as the dihydrochloride of N-phenyl-piperasino-N'-n-propyl acetate.

Di-hydrochloride of N-phenyl-piperazino-N'-n-propyl acetate

8 grams of vacuo-distilled N-phenyl-piperazino-N'-n-propyl acetate are dissolved in 150 cc. of ether and anhydrous hydrogen chloride gas is bubbled in until precipitation is complete. The yield is ninety per cent (9grams).

The di-hydrochloride of N-phenyl-piperazino-N'-n-propyl acetate is purified for analysis by successive crystallisations from n-butanol. It is soluble in water and ethanol. The compound is oven-dried at 105° for six hours prior to analysis.

Calculated for $C_{15}H_{22}O_2N_2 \cdot 2HCl$: N, 8.36. Found: N, 8.43.

N-Phenyl-piperazino-N'-n-butyl acetate

32.4 grams (0.2 mol) of N-phenyl-piperazine²³, 30.1 grams (0.2 mol) of n-butyl chloroacetate^{13,15} and 31.8 grams (0.5 mol) of sodium carbonate are suspended in 100 cc. of 95% ethanol. The resulting suspension is refluxed vigorously on the water bath for two hours and filtered. Evaporation of the ethanol leaves a yellow oil which solidifies when chilled in an ice bath. The cream-colored solid is taken up in ether and the resulting ethereal solution is filtered from a small amount of sticky solid. Evaporation of the ether leaves crude N-phenyl-piperazino-N'-n-butyl acetate which is still contaminated with traces of N-phenyl-piperazine. Distillation in vacuo removes the latter. N-phenyl-piperazino-N'-n-butyl acetate boils at 218-220° at 8-9 mm. (bath temperature, 270°). The average yield is eighty per cent. The distillate contains a trace of color due to slight decomposition, that attends the distillation. The product is dissolved in cold, dilute hydrochloric acid, filtered and cooled in an ice bath. An excess of

dilute sodium hydroxide is added and the white precipitate thus formed is filtered by suction and washed with cold water. The process of solution in dilute hydrochloric acid and reprecipitation by means of dilute sodium hydroxide is repeated. The white solid is then dried between porous plates and shaken with ether. The ether dissolves most of the compound leaving a small amount of an oily scum from which the solution is decanted. The ethereal solution is dried over anhydrous sodium sulfate, filtered and evaporated in a current of air. The crystalline residue is *N*-phenyl-piperasino-*N'*-*n*-butyl acetate which melts at 54-54.5°. The process of solution in ether followed by drying over anhydrous sodium sulfate is repeated; the resulting *N*-phenyl-piperasino-*N'*-*n*-butyl acetate has its melting point unchanged.

N-phenyl-piperasino-*N'*-*n*-butyl acetate is a white crystalline solid that is insoluble in water and soluble in the common organic solvents. The pure compound boils at 218-220° at 3-9 mm. (bath temperature, 270°) and melts at 54-54.5°.

Calculated for $C_{16}H_{24}O_2N_2$: N, 10.14. Found: N, 10.02.

N-Phenyl-piperasino-*N'*-ethenamide

32.4 grams (0.2 mol) of *N*-phenyl-piperasino²³, 18.7 grams (0.2 mol) of chloroethenamide^{16,17,18,21} and 21.2 grams (0.2 mol) of sodium carbonate are refluxed in 100 ml. of toluene on an oil bath for two hours. The reaction which sets in soon after heat is applied to the bath is very violent. After the reaction is over, the sluggish, suspension is poured into a beaker and the toluene is removed by careful evaporation. The solid mass is cooled and stirred vigorously with 100 cc. of cold water to remove the inorganic salts. The desired compound, a white solid that is very insol-

uble in cold water, is recovered by filtration. The yield is quantitative.

N-phenyl-piperazino-N'-ethanamide is soluble in hot water, hot benzene, hot toluene, hot diamyl ether and hot hexone (4-methyl-pentanone-(2)). It crystallizes from these solvents on cooling. The compound is soluble in ethanol, n-butanol, dioxan (diethyleneoxide) and cellosolve (1-ethoxy-ethanol-(2)). It is insoluble in ethyl ether and isopropyl ether. N-phenyl-piperazino-N'-ethanamide can be satisfactorily crystallised from toluene, benzene or water in order of their listing. Repeated crystallisations from toluene give crystals which melt at 169-170°. When toluene is used as a solvent, the solution must be filtered rapidly through a funnel heated by a steam coil or through a pre-heated Büchner funnel. This is necessary because the compound is extremely soluble in toluene at the boiling point of the solvent, but slight cooling produces voluminous precipitation.

Calculated for $C_{12}H_{17}ON_3$: N, 19.17. Found: N, 19.12.

Conversion of N-phenyl-piperazino-N'-ethyl acetate into N-phenyl-piperazino-N'-ethanamide

N-phenyl-piperazino-N'-ethanamide is also prepared by the action of concentrated ammonium hydroxide on N-phenyl-piperazino-N'-ethyl acetate. 5 grams of the ester, purified by distillation in vacuo, are shaken with 40 cc. of concentrated ammonium hydroxide in a glass-stoppered bottle and allowed to stand with occasional shaking in the ice-box for six to eight hours. N-phenyl-piperazino-N'-ethanamide precipitates out in eighty-five per cent yield. Successive crystallisations from toluene yield a product which melts at 169-170°. A mixed melting point with an authentic specimen

of *N*-phenyl-piperasino-*N'*-ethanamide shows no depression. The two compounds are exactly alike in all of their properties.

Calculated for $C_{12}H_{17}ON_3$: N, 19.17. Found: N, 19.22.

N-Phenyl-piperasino-*N'*-ethanenitrile

16.2 grams (0.1 mol) of *N*-phenyl-piperasine²³ are dissolved in 50 cc. of 95% ethanol and 8 cc. of 40% methanal are added with stirring. After an hour a solution of 6.5 grams (0.1 mol) of potassium cyanide in 19 cc. of water is added followed by a solution of 6 grams (0.1 mol) of acetic acid in 30 cc. of water (HOOB !). The resulting solution is stirred thoroughly and allowed to stand twenty-four hours. The solution is then made alkaline with sodium carbonate and cooled in an ice bath, whereby crystals of *N*-phenyl-piperasino-*N'*-ethanenitrile separate out. At this point some unchanged *N*-phenyl-piperasine separates out as a yellow oil; it is removed, dissolved in 95% ethanol and subjected again to the methanal-potassium cyanide-acetic acid treatment described above. In both cases the ethanol is removed from the alkaline solutions in a current of air and the crystals obtained are combined. This procedure results in a yield of forty per cent. The total yield can be progressively increased by repeating the above treatment, but it is more feasible to synthesize the compound by the procedure described in the next section. The properties of *N*-phenyl-piperasino-*N'*-ethanenitrile are exactly like these of the compound obtained by the action of *N*-phenyl-piperasine²³ on chloroethanenitrile^{17,19,20}; they are discussed below.

N-phenyl-piperasino-*N'*-ethanenitrile obtained in this synthesis is purified by repeated crystallization from hexane. It melts at 65-65.5°.

Calculated for $C_{12}H_{15}N_3$: N, 20.89. Found: N, 20.70.

16.2 grams (0.1 mol) of N-phenyl-piperazine²³, 7.6 grams (0.1 mol) of chloroethanenitrile^{17,19,20} and 15.9 grams (0.15 mol) of sodium carbonate are mixed in 100 cc. of hexane. Considerable heat is evolved. The suspension is refluxed vigorously on the water bath for an hour and filtered while hot. The cooled residue of inorganic salts is repeatedly washed with ether; the latter is filtered and evaporated to dryness in a current of air. The solid thus obtained is added to that remaining in the evaporation of the original hexane solution. The total yield of N-phenyl-piperasino-N'-ethanenitrile is seventy per cent of theoretical.

N-phenyl-piperasino-N'-ethanenitrile is insoluble in water and soluble in cold ether, ethanol, propanone, isopropyl ether, benzene, dioxan (diethylene oxide), ethyl acetate, trichloromethane and tetrachloromethane. It is soluble in hot hexane and very insoluble in cold hexane. It is purified by successive crystallisations from hexane. N-phenyl-piperasino-N'-ethanenitrile melts at 65-65.5°. A mixed melting point with a specimen obtained in the independent synthesis described in the preceding section shows no depression.

Calculated for $C_{12}H_{15}N_3$: N, 20.89. Found: N, 20.71.

Reduction of N-phenyl-piperasino-N'-ethyl acetate

N-phenyl-piperasino-N'-ethyl acetate is purified for this reaction by distillation in vacuo. The n-butanol is obtained anhydrous just prior to use by fractional distillation through an efficient column; the first one hundred cc. of the distillate are rejected and the fraction boiling at 117-118° is collected.

The reaction is carried out in a two-neck flask to which is attached a long, water-cooled condenser. The top of the latter is fitted with a calcium chloride tube.

It is absolutely essential that the above precautions be observed. Failure to use reagents of high purity and anhydrous media causes the yields to be cut severely.

24.8 grams (0.1 mol) of N-phenyl-piperasino-N'-ethyl acetate are dissolved in 400 cc. of freshly distilled n-butanol and the solution is poured into a two-neck flask of liter capacity to which has been fitted a long, water-cooled condenser as indicated above. 14 grams (0.6 mol) of sodium cut in large chunks (about four pieces, each the size of one's thumb) are dropped in rapidly. The flask is surrounded by an ice bath until the initial vigorous reaction has subsided; the freezing mixture is then removed and the reaction is allowed to proceed without external cooling. The flask is heated on an oil bath (bath temperature, 150°) until all of the sodium has disappeared (average time, three hours), care being taken to maintain anhydrous conditions throughout. After cooling somewhat, 100 cc. of water are added and all of the n-butanol is removed by rapid steam distillation. The strongly alkaline solution (volume, 100 cc.) that remains in the flask is now repeatedly extracted with hot benzene. The latter is separated, cooled and dried over anhydrous sodium carbonate. Filtration of the benzene solution followed by evaporation leaves an oil which soon solidifies. The yield of N-phenyl-piperasino-N'-beta-ethanol is thirty-five per cent. Repeated crystallisation from hexane accompanied by decolorization with norite yields long, white needles which melt at 82-82.5°. A mixed melting point determination with an authentic specimen

of *N*-phenyl-piperasino-*N'*-beta-ethanol (m.p. 82.5-83°), prepared by an independent synthesis and purified in similar fashion, gives a value of 82.5-83°.

N-Phenyl-piperasino-*N'*-sodium acetate

After the concentrated alkaline solution resulting from the reduction of *N*-phenyl-piperasino-*N'*-ethyl acetate has been repeatedly extracted with hot benzene, it is heated on a steam bath in a current of air until all of the benzene has been removed. Enough water is added at the boiling point to dissolve all of the solid present and the solution is boiled with norite. Filtration followed by cooling yields white crystals of *N*-phenyl-piperasino-*N'*-sodium acetate. They are soluble in hot water and insoluble in the common organic solvents. The compound is purified by repeated crystallization from water. Prior to analysis *N*-phenyl-piperasino-*N'*-sodium acetate is dried in an oven at 105° for six hours.

Calculated for $C_{12}H_{15}O_2NNa$: N, 11.57. Found: N, 11.39.

16.2 grams (0.1 mol) of *N*-phenyl-piperasine²³, 11.7 grams (0.1 mol) of sodium chloroacetate^{22,26} and 15.9 grams (0.15 mol) of sodium carbonate are suspended in 100 cc. of water. The reaction solution is refluxed over a free flame until evolution of CO₂ has ceased and oily drops of *N*-phenyl-piperasine are no longer visible (average time, one hour). The hot, clear solution is filtered and cooled. White crystals of *N*-phenyl-piperasino-*N'*-sodium acetate are formed in quantitative yield. The compound is recrystallized a second time from water and washed with a small amount of ethanol to remove the last traces of *N*-phenyl-piperasine. It is likewise oven-dried for six hours at 105° prior to analysis. *N*-

phenyl-piperazino-N'- sodium acetate is identical in all of its properties to the compound obtained as a by-product in the reduction of N-phenyl-piperazino-N'-ethyl acetate.

Calculated for $C_{12}H_{15}O_2N_2Na$: N, 11.57. Found: N, 11.48.

SUMMARY

1. The following new compounds have been prepared and characterized:

- (1) Piperasino-1,4-bis (n-propyl acetate). (30)^a
- (2) Di-acidsulfate of piperasino-1,4-bis (n-propyl acetate). (31)
- (3) Piperasino-1,4-bis (n-butyl acetate). (32)
- (4) Di-acidsulfate of piperasino-1,4-bis (n-butyl acetate). (32)
- (5) Piperasino-1,4-bis (n-hexyl acetate). (33)
- (6) Di-acidsulfate of piperasino-1,4-bis (n-hexyl acetate). (34)
- (7) n-Hexyl chloroacetate. (35)
- (8) N-phenyl-piperasino-N'-ethyl acetate. (42)
- (9) Dihydrochloride of N-phenyl-piperasino-N'-ethyl acetate. (43)
- (10) Sulfate of N-phenyl-piperasino-N'-ethyl acetate. (43)
- (11) N-phenyl-piperasino-N'-methyl acetate. (44)
- (12) Dihydrochloride of N-phenyl-piperasino-N'-methyl acetate. (44)
- (13) N-phenyl-piperasino-N'-n-propyl acetate. (45)
- (14) Dihydrochloride of N-phenyl-piperasino-N'-n-propyl acetate. (46)
- (15) N-phenyl-piperasino-N'-n-butyl acetate. (46)
- (16) N-phenyl-piperasino-N'-ethanamide. (47)
- (17) N-phenyl-piperasino-N'-ethanenitrile. (49)
- (18) N-phenyl-piperasino-N'-beta-ethanol. (50)
- (19) N-phenyl-piperasino-N'-sodium acetate. (52)

(a) Numbers in parentheses following each title indicate the appropriate pages on which the material is found.

2. The following compounds have been synthesized by new and improved methods and have been characterized:

- (1) Piperazino-1,4-bis (ethyl acetate). (27)
- (2) Di-acidsulfate of piperazino-1,4-bis (ethyl acetate). (27)
- (3) Piperazino-1,4-bis (methyl acetate). (29)
- (4) Di-acidsulfate of piperazino-1,4-bis (methyl acetate). (29)
- (5) Piperazino-1,4-bis (ethanamide). (35)
- (6) Piperazino-1,4-bis (ethanenitrile). (37)
- (7) Di-acidsulfate of piperazino-1,4-bis (acetic acid). (38)
- (8) Piperazino-1,4-bis (acetic acid). (39)
- (9) Piperazino-1,4-bis (sodium acetate). (41)
- (10) Piperazino-1,4-bis (beta-ethanol). (40)

3. The conversion of piperazino-1,4-bis (ethyl acetate) into piperazino-1,4-bis (ethanamide) has been effected. (35)

4. The conversion of piperazino-1,4-bis (ethyl acetate) into piperazino-1,4-bis (acetic acid) has been depicted. (39)

5. The conversion of piperazino-1,4-bis (ethanamide) into piperazino-1,4-bis (acetic acid) has been depicted. (38)

6. The dehydration of piperazino-1,4-bis (ethanamide) to piperazino-1,4-bis (ethanenitrile) has been accomplished. (38)

7. The reduction of piperazino-1,4-bis (ethyl acetate) to piperazino-

1,4-bis (beta ethanol) has been achieved. (40)

8. The conversion of N-phenyl-piperazino-N'-ethyl acetate into N-phenyl-piperazino-N'-ethanamide has been effected. (48)

9. The reduction of N-phenyl-piperazino-N'-ethyl acetate to N-phenyl-piperazino-N'-beta-ethanol has been described. (50)

10. A comparison has been made between the series of compounds of piperazine and various derivatives of monochloroacetic acid and the series of compounds of N-phenyl-piperazine and various derivatives of monochloroacetic acid. (14)

11. N-Hexyl chloroacetate has been synthesized and its properties reported. (35)

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BIBLIOGRAPHY

- (1) Adelson, M.S. Thesis, University of Florida, 1933.
- (2) Pollard and Adelson, J. Am. Chem. Soc., 56, 150 (1934).
- (3) Pollard, Adelson and Bain, J. Am. Chem. Soc., 56, 1759 (1934).
- (4) Pollard, Bain and Adelson, J. Am. Chem. Soc., 57, 199 (1935).
- (5) Van Dorp, Rec. trav. Chim., 29, 69 (1909).
- (6) Franchimont and Kramer, Rec. trav. chim., 31, 40 (1912).
- (7) Munch, Ber., 29, 62 (1896).
- (8) Franchimont and Kramer, Proc. K. Akad. Wetensch. Amsterdam, 12, 452 (1909).
- (9) Proleg and Blazek, Collection Czechoslov. Chem. Communications, 6, 549 (1934).
- (10) Beilstein--Handbuch der organischen Chemie, Springer, Berlin, 1920 (4th edition), Vol. II, p. 197.
- (11) Conrad, Ann., 188, 218 (1877).
- (12) Henry, Ber., 6, 742 (1873).
- (13) Beilstein--Handbuch der organischen Chemie, Springer, Berlin, 1920 (4th edition), Vol. II, p. 198.
- (14) Schreiner, Ann., 197, 8 (1879)
- (15) Gehring, Bull. soc. chim., [2] 46, 147 (1886).
- (16) Beilstein--Handbuch der organischen Chemie, Springer, Berlin, 1920 (4th edition), Vol. II, p. 199.
- (17) Scholl, Ber., 29, 2417 (1896)
- (18) Organic Syntheses--John Wiley and Sons, Inc., New York, 1927, Vol. 7, p. 16.

- (19) Beilstein--Handbuch der organischen Chemie, Springer, Berlin, 1920
(4th edition), Vol. II, p. 201.
- (20) Bauer, Ann., 229, 166 (1885).
- (21) Träger and Hille, J. prakt. Chem., (2) 71, 204 (1905).
- (22) Kastle and Keiser, Am. Chem. J., 18, 472 (1893).
- (23) Pollard and MacDowell, J. Am. Chem. Soc., 56, 2199 (1934).
- (24) Patterson, J. Am. Chem. Soc., 55, 3905 (1933).
- (25) Pollard, Bain and Adelson, C.A. 29, 1425 (1935).
- (26) Beilstein--Handbuch der organischen Chemie, Springer, Berlin, 1920
(4th edition), Vol. II, p. 196.
- (27) Adelson, MacDowell and Pollard, unpublished work.
- (28) Abderhalden and Rossner, Z. physiol. Chem., 144, 219 (1925).
- (29) Jacobi, Ber. 66B, 113 (1933).
- (30) Herz, Ber., 30, 1584 (1897).
- (31) Watanson, Ann., 92, 49 (1854); 98, 291 (1856).
- (32) Meyer-Jacobson, Lehrbuch der organischen Chemie, De Gruyter, Berlin,
1923, Vol. II, Part 3, p. 1347.
- (33) Schmidt and Wichman, Ber., 24, 3237 (1891).
- (34) Bischoff, Ber., 25, 2940 (1892).
- (35) v. Braun, Coll and Zobel, Ber., 59B, 936 (1926).
- (36) Meyer and Meyer, Ber., 52, 1249 (1919).
- (37) Raiford, C.A., 16, 898 (1922).
- (38) Moore, Boyle and Thorn, J. Chem. Soc., 1929, 39.

BIOGRAPHY

David E. Adelson was born March 21, 1912, at Chicago, Illinois. He received his pre-collegiate training in the public schools of Tampa, Florida. He was graduated from the University of Florida in 1932 with the Degree of Bachelor of Science and received the Degree of Master of Science from the same institution in 1933. He has attended the University of Florida continuously from 1928 to the present.

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COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee, and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

Date August 30, 1935

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